Genetic testing in developmental disorders, now and in the future: a case-based guide

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Abstract

Genomic testing is now routine in the assessment of paediatric developmental disorders, with whole genome sequencing (WGS) increasingly used as a first-line investigation in England. Rapid advances in genomic technologies and mainstreaming genomics have transformed clinical practice, while introducing practical and interpretive challenges for paediatricians. Using illustrative clinical cases, this article explores some key areas of testing complexity, including dynamic testing pathways, uncertain or negative results and the growing value of genome re-analysis. We consider how emerging technologies and collaborative models of care may influence future diagnostic and management approaches. This short guide supports the paediatric application of genomic testing as a clinical tool that will continue to evolve. Recognising the availability, clinical utility and limitations of genomic testing, alongside timely access to specialist support, is key to maximising the benefits of genomic advances for children with developmental disorders and their families. We provide practical actions for test selection, consent, and interpreting negative/uncertain results.

Keywords developmental disorders; genomic testing; whole genome sequencing

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Introduction and background

Developmental disorders are a common focus of paediatric practice, contributing substantially to clinical workload across community and hospital settings. Although individual conditions are often rare, UK birth cohort data indicate that up to 11% of children may receive a diagnosis of a developmental disorder by late childhood.[1]

For many children, developmental differences arise from complex interactions between genetic and environmental influences. The underlying genetic architecture is highly heterogeneous, spanning chromosomal (including aneuploidy, structural rearrangements, copy number variants) and monogenic disorders, imprinting defects, germline vs mosaic or somatic changes, dual or multiple diagnoses, and polygenic mechanisms.[2,3] This heterogeneity and ongoing discovery of new genes and genetic mechanisms pose diagnostic challenges that drive repeated investigation and long-term prognostic uncertainty for patients and their families.

Genetic testing for children with developmental disorders in England has evolved rapidly over recent years. Earlier diagnostic pathways relied on karyotyping and targeted tests which were limited in scope and efficiency.[4] Chromosomal microarray techniques enabled higher-resolution detection of copy number variants and, until recently, formed part of first-line testing for children with developmental delay and intellectual disability.

Gene sequencing technologies have since expanded genomic analysis to single-base resolution, allowing interrogation of single genes, targeted gene panels, whole exomes and ultimately the whole genome. Large-scale UK research initiatives such as the Deciphering Developmental Disorders (DDD) study (https://www.deciphergenomics.org/) and 100 000 Genomes Project (100kGP; (https://www.england.nhs.uk/genomics/genomic-research/100000-genomes-project/), provided evidence of clinical utility and feasibility to embed genomic sequencing within routine NHS care.

Whole genome sequencing (WGS) generates a large genomic dataset, but clinical interpretation is targeted. Analysis is restricted to one or more curated and regularly updated virtual gene panels, selected according to clinical phenotype. These may collectively cover large portions of the genome, but do not represent an unrestricted genome analysis in its entirety. The WGS data is stored to enable further updated existing gene panel analysis and re-analysis against newer gene panels in the future.

The UK National Health Service (NHS) is the first national healthcare system in the world to offer WGS as part of routine care for rare disease diagnosis including developmental disorders.[5] Non-genetic medical specialists, including paediatricians, can request genomic testing for certain clinical indications, known as mainstreaming.[6]

In England, genomic testing is delivered through the nationally commissioned Genomic Medicine Service, with standardised pathways and eligibility defined by the National Genomic Test Directory and testing undertaken by seven Genomic Laboratory Hubs (GLHs).

These advances have shown substantially improved diagnostic yields, particularly when trio analysis using parental

samples is utilised.[4,7] Currently, we are achieving a genetic diagnosis in up to 40% of probands being tested.[8] Earlier diagnosis can improve access to personalised care, therapy, support and wider reproductive counselling.

Paediatricians often work closely with clinical geneticists to manage rare genomic conditions in children as part of a multidisciplinary approach. They can play a crucial role in embedding genomic medicine into the daily clinical practice by facilitating genomic testing, seeking informed consent, support participation in research and dealing with the genomic report. Even when a referral is made to clinical genetics, paediatricians often still play a leading role in providing continuity of care to children with genomic conditions.

However, this shift in service delivery has altered approaches to genetic consent, counselling and result interpretation within paediatric practice. This has placed increasing demands on clinicians to keep pace with changing testing pathways and growing interpretive complexities. UK survey data indicate that, as genomic testing has been rapidly mainstreamed, gaps remain between service expectations and paediatricians' confidence in certain aspects of genomic practice.[6]

Using illustrative cases, this practical guide aims to support paediatricians in navigating these issues and in accessing appropriate specialist support within an evolving genomic service.

Case 1: a boy with autism, learning differences and subtle dysmorphic features

A six-year-old boy was referred to community paediatrics due to concerns regarding social communication difficulties, unusual behaviours, and impaired learning progress within a mainstream school. He had previously been assessed in infancy for mild global developmental delay, including motor and speech concerns, but did not require ongoing follow-up.

There was a family history of maternal ADHD, a maternal uncle with learning difficulties, and dyslexia and autism in wider family members. On examination he had subtle dysmorphic features and chromosomal microarray and Fragile X (FRAX) testing were requested in keeping with previous practice. However, under updated NGTD criteria, this testing was declined by the local GLH and DNA was stored only.

WGS enables genome-wide detection of copy number variants alongside single-gene analysis within a single test, now restricting microarray eligibility. Standalone Fragile X testing has been removed from the NGTD due to persistently low diagnostic yield (less than 1%), except in certain circumstances, such as targeted testing for where there's a known diagnosis of Fragile X in the family or strong clinical suspicion (see Figure 1). Following a discussion with clinical genetics, trio WGS was recommended using a broad multi-panel analysis approach.

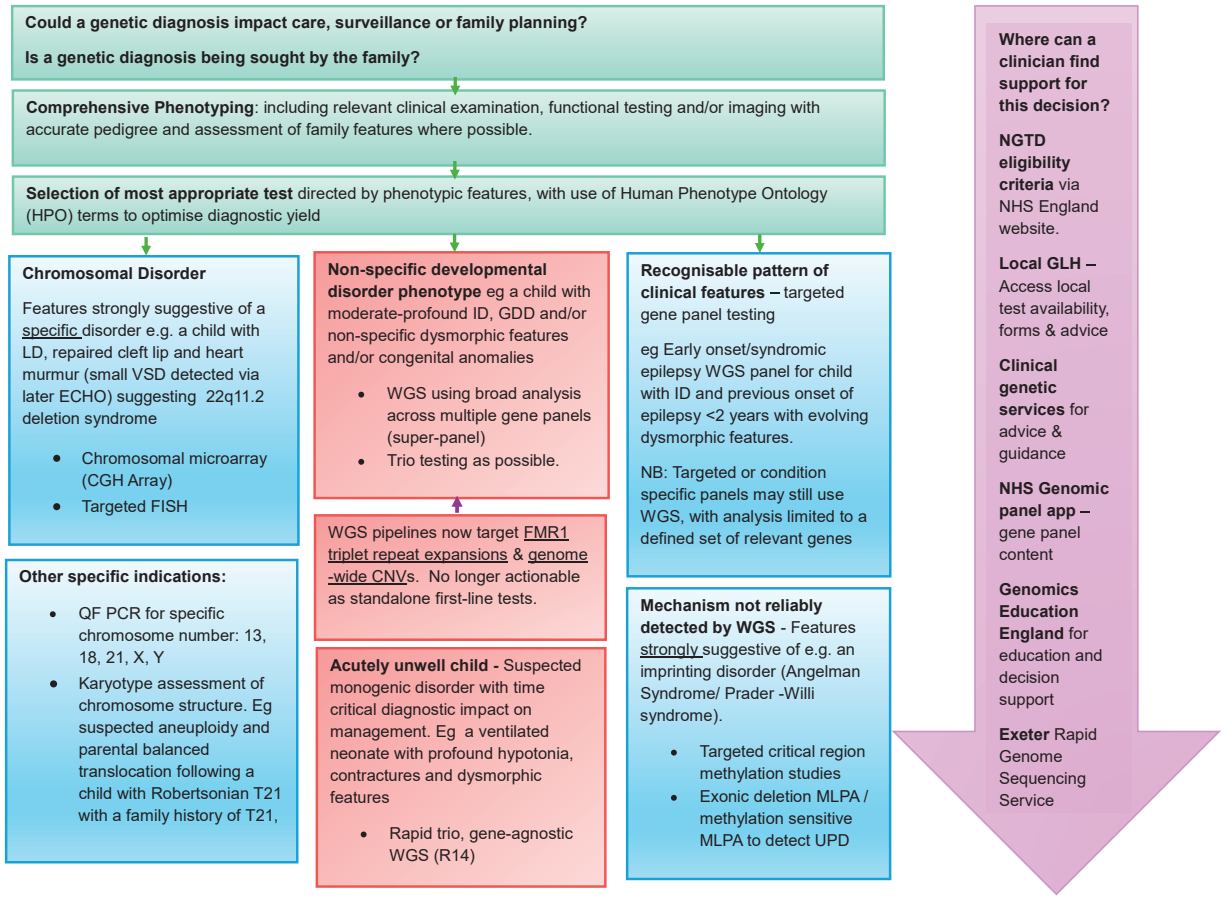

Figure 1 An overview of current genomic testing pathways for children with suspected developmental disorders. This illustrates contemporary testing availability and is not intended to be exhaustive.

The paediatrician had completed appropriate training to support mainstreamed pre-test counselling and consent, and trio WGS was arranged via the expanded paediatric disorders (R27) pathway. The result did not identify a pathogenic or likely pathogenic variant to explain the child's presentation, and no clinically actionable additional findings were reported.

The family were counselled regarding the implications of a negative result (see Figure 2). Re-referral for review of genetic testing may be appropriate in future, with re-analysis usually considered after a defined interval (at least 3 years) or if new clinical features emerge (see case 3).

Practice points: genomic testing pathways are dynamic

- A negative report does not exclude a genetic diagnosis and re-analysis of WGS data is possible after a period of time if a monogenic diagnosis is still strongly suspected.
- Genomic testing pathways are reviewed periodically, with NGTD criteria updated in line with technological and diagnostic advances.
- Recent updates have streamlined testing for non-specific developmental disorder phenotypes, favouring a broader WGS first-line approach to reduce fragmented testing and diagnostic delay.

Logistics of organising testing

Record of Discussion forms for WGS and non-WGS are available from GMS and local GLH

Training for taking consent provided through Genomics Education England toolkit

Rapid WGS testing for the acutely unwell patient requires a distinct consent and test order form available from the Exeter GLH

National Genomic Research Library (NGRL)

Secure research resource of de-identified genomic and health data.

Supports approved research to improve diagnosis, understanding of disease and development of new treatments

Participation is optional, patients may choose not to take part, defer the decision or withdraw at any time without affecting NHS genomic testing

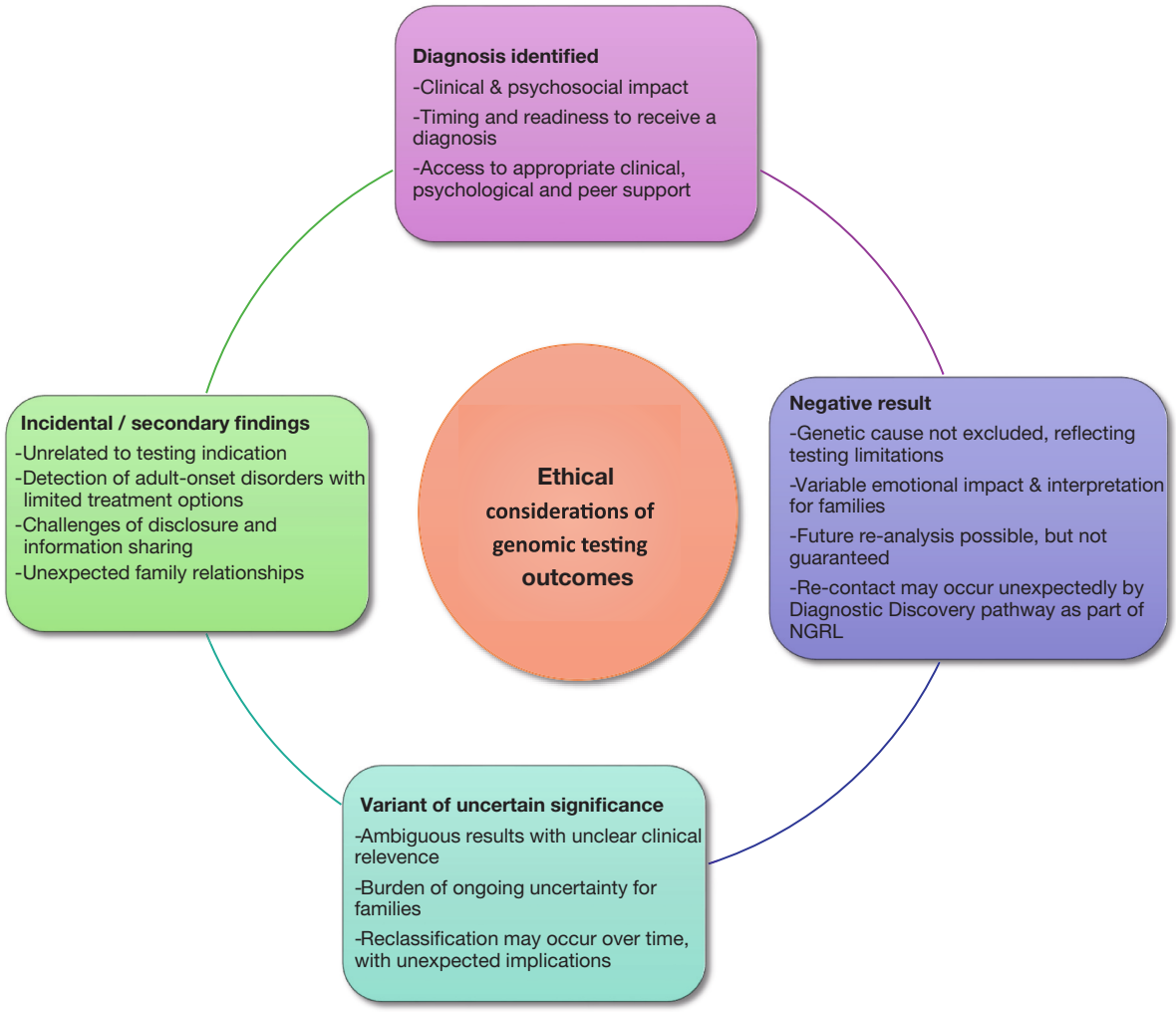

Figure 2 Summary of the practicalities of organising WGS and the ethical and family considerations surrounding the possible outcomes of testing.

- Clinicians should anticipate that test availability and eligibility criteria will change over time. Staying updated via the local Clinical Genetics service, NGTD and local GLH supports accurate counselling and reduces declined requests.
- Gene coverage of commissioned panels can be explored via the NHS GMS PanelApp resource (see further resources). The gene content of the existing panels are updated regularly where the numbers can decrease as well as increase. New panels can also be created.
- Implementation of NGTD updates may vary between GLHs, and alongside local clinical genetics services, they provide region-specific support in applying testing criteria.

Case 2: a girl with global developmental delay (GDD) and familial variant of uncertain significance (VUS)

A two-year-old girl was referred for paediatric assessment of global developmental delay. She was born at term to healthy, non-consanguineous parents of Pakistani origin. There was a family history of neurodevelopmental delay in an older sibling, who carried a maternally inherited chromosomal microdeletion reported as a VUS. Targeted testing to aid VUS interpretation, confirmed the same variant in the proband.

In addition to developmental delay, she had early infant feeding difficulties, episodic eczematous and seborrhoeic rash, and slow growth of hair and nails with occasional breakage. An opinion sought from clinical genetics, concluded that the familial microdeletion remained unlikely to be causative.

Given the significant phenotype, broad R27 paediatric super-panel trio WGS was undertaken to investigate an alternative genetic diagnosis. This identified compound heterozygous variants in the *BTD* gene, consistent with autosomal recessive partial biotinidase deficiency. Urgent biochemical testing confirmed reduced plasma biotinidase activity.

Oral biotin supplementation was commenced with improvement in skin and nail features. She was referred to a tertiary metabolic service, and the family re-referred to clinical genetics for counselling and sibling testing.

Practice points: early recognition of treatable genetic conditions

- Inborn errors of metabolism (IEM) are a potentially treatable cause of developmental disorders; early recognition is essential to prevent deterioration and irreversible harm in some cases.
- Where clinically indicated, undertake biochemical phenotyping alongside genomics testing to enable faster diagnosis, interpretation of variants and guide targeted testing (e.g. metabolic-specific WGS over broad multi-panels).
- In acutely unwell children, including those with rapid developmental regression, rapid WGS (i.e. R14) may be initiated by paediatric teams with clinical genetics input. Trio testing is preferred to enable a gene-agnostic analysis and accurate phenotyping is essential to maximise diagnostic yield. This requires specialist approval from the local Clinical genetics service and Exeter GLH (see further resources).
- Genomic testing should not delay or replace urgent biochemical investigations or initial management (see British Inherited Metabolic Disease Group guidance).

Future practice

Expansion of population level WGS initiatives such as The Generation Study[9] will likely increase referrals for diagnostic confirmation and family follow-up of actionable childhood-onset conditions.

Practice points: VUS

- A VUS reflects insufficient evidence to determine whether a variant has a benign or pathogenic clinical effect.
- VUS's are not clinically actionable and should not be used to guide diagnosis, management, or family predictive genetic testing. Family testing may be appropriate only where it could support variant reclassification (i.e. segregation analysis with phenotyping or confirmation of a *de novo* variant).
- Where the phenotype remains unexplained, further genomic testing or re-analysis could be considered to pursue an alternative diagnosis.
- The possibility of VUS result is a core component of pre-test counselling and consent (Figure 2).

Case 3: a child with global developmental delay (GDD), hypotonia and seizures and a diagnosis made on genome re-analysis

A four-year-old child was referred to paediatrics with global developmental delay, marked speech and language delay, hypotonia, microcephaly, and seizures. The perinatal and family history was unremarkable. The child has distinctive facial features.

Initial genetic testing was undertaken via broad R27 paediatric super-panel trio WGS. No pathogenic or likely pathogenic variants were identified, and a genetic diagnosis was not confirmed. The family were counselled regarding the limitations of current genomic knowledge and technology and the possibility that a genetic diagnosis might not yet have been identified.

Over the following years, the child continued to show developmental difficulties, with evolving features including motor coordination problems and learning differences. No alternative acquired or metabolic cause was identified.

Subsequently, following the description of a newly recognised neurodevelopmental disorder associated with pathogenic heterozygous variants in *RNU4-2*, re-analysis of the existing WGS data was undertaken through the Diagnostic Discovery pathway at Genomics England. This identified a *de novo* pathogenic *RNU4-2* variant consistent with the child's clinical presentation. This gene was not analysed at the time of the original analysis, as *RNU4-2* was not yet recognised as an established disease—gene association. Heterozygous *RNU4-2* variants have been reported in 2024 to be associated with RNU4-2—related neurodevelopmental disorder (RENU syndrome), one of the most prevalent monogenic neurodevelopmental disorders.[10,11]

The family were re-contacted and referred back to clinical genetics for post-results counselling.

Practice points: evaluation of negative genomic results and the value of genome re-analysis

- A negative genomic result does not exclude a genetic diagnosis (Figure 2). A causative variant may not be identified at the initial genomic analysis due to several factors including

limitations of the current knowledge of gene—disease associations, technical limitations of the analysis pipelines, the scope of panel selection, or evolving clinical findings that may not have been evident at the time of initial analysis.
- Genomic knowledge is rapidly evolving, with new gene—disease associations continuously identified. Variants may be present in existing genomic data but remain not prioritised or evaluated at the time of initial analysis.
- The retrospective re-analysis of existing WGS data can provide new genetic diagnoses for patients who did not receive a genetic diagnosis at the time of the initial WGS analysis, through the NHS Diagnostic Discovery pathway, where potential new findings from ongoing analysis of WGS data by the internal Genomics England work and researchers on the NGRL are returned to the GLHs for evaluation and reporting. In addition, re-analysis of individual cases could be considered if new clinical information emerges. Re-analysis of WGS data from individual cases can only be requested by clinical genetics currently and therefore, if the paediatrician wishes to consider this, they need to contact the clinical genetics team.
- Clinicians should consider the need for alternative genetic testing for conditions with mechanisms which may not be detected by standard WGS bioinformatic pipelines such as short tandem repeat (STR) disorders (such as myotonic dystrophy), imprinting disorders/uniparental disomy (such as Angelman or Prader—Willi syndromes, balanced structural variants (such as balanced translocations), mosaic disorders requiring ultra-deep sequencing (e.g. PIK3CA-related segmental overgrowth disorder) and mitochondrial genome analysis.
- While WGS would capture the data necessary to identify pathogenic variants, their detection depends on the bioinformatic pipeline and genomic analysis. Clinicians are encouraged to consult with their local Clinical Genetics service and GLH clinical scientists to determine if further testing to detect such variants is indicated.
- These considerations are important in post-test counselling following a negative genomic result.

Summary, future directions and conclusion

Developmental disorders are commonly encountered in paediatric practice and frequently require genetic investigation. Advances in genomic technologies and service delivery have transformed diagnostic pathways, with WGS now part of the mainstream genomic evaluation of children with developmental disorders.

Genomic testing pathways are dynamic, with eligibility criteria and testing strategies evolving in response to technological and diagnostic advances. A negative genomic result does not exclude a genetic diagnosis due to limitations in current knowledge, pipeline analysis, and evolving phenotypes, which means that a genetic diagnosis may only become evident following re-analysis of genomic data (Box 1). The family's diagnostic odyssey may be weeks, months or over many years. Treatable genetic conditions, including inborn errors of metabolism, should be considered, and genomic testing should complement rather than delay appropriate biochemical investigations and clinical management.

As genomic testing becomes increasingly embedded within mainstream paediatric practice, collaborative models of care would be essential. These include a close working relationship with local Genetics services by accessible communication channels, informally by emails and more formally by letters and regular MDT meetings and educational sessions.

Multidisciplinary team (MDT) working between paediatricians, clinical geneticists, clinical scientists, metabolic specialists, paediatric neurologists, and allied health professionals supports appropriate testing strategy, shared decision-making, deep phenotyping, interpretation of complex, negative or uncertain results and structured framework for diagnosis and coordinated care.

Common pitfalls in genomic testing for developmental disorders

- Assuming a negative genomic result excludes a genetic cause: A negative WGS result reflects current knowledge and pipeline and interpretation limitations. Genetic diagnoses may be evident only after re-analysis or as phenotypes evolve.
- Over-interpreting a Variant of Uncertain Significance (VUS): VUS are not diagnostic and should not be used as a confirmed diagnosis to guide management or cascade family testing unless further reclassified following additional evidence.
- Inadequate or non-specific phenotyping at the time of test request: Limited clinical data reduces variant prioritisation and diagnostic yield.
- Use of no-longer first-line tests: Genetic testing pathways are evolving. Investigations such as chromosomal microarray or standalone Fragile X testing may not be first-line in many current scenarios. Awareness of local NGTD implementation helps avoid declined or delayed testing.
- Not considering genetic mechanisms that may require alternative testing: STR disorders, imprinting defects/uniparental disomy, balanced structural rearrangements, mosaic disorders, and mitochondrial DNA disorders may not be reliably detected through standard WGS pipelines and may require additional or targeted testing. If a familial gene variant is known, then targeted testing for the single variant is more time-efficient (weeks vs months for results).
- Delaying urgent biochemical investigations while awaiting genomic results: In suspected inborn errors of metabolism or acute neurological presentations, genomic testing should complement, not delay, immediate biochemical investigations, as indicated.
- Not explaining the risk of incidental findings or unexpected results: The record of discussion form for any broad genetic testing covers the possibility of incidental findings. Incidentally discovered pathogenic germline genetic variants refer to the finding of a pathogenic variant in a gene that is unrelated to the reason for the initial test and is not actively sought. These include pathogenic variants in cancer predisposition genes such as *BRCA1* (associated with breast and ovarian cancer) or *RET* (associated with Multiple endocrine Neoplasia type 2 or MEN2) with widespread implications in a family. The risk of these findings should be actively discussed when taking consent and in the event one is reported, a referral to Clinical Genetics is recommended.
- Not explaining that the parental relationships will be confirmed when performing trio analysis: There is always the risk of non-paternity or non-maternity (the latter especially with IVF conceptions abroad) and this may not be evident to families when trio analysis is taking place.

Box 1

Although short-read WGS has substantially improved the diagnostic yield, limitations remain. Emerging technologies include long-read sequencing with improved detection of complex structural variants, repeat expansions, mosaicism and imprinting disorders, and phase of apparent biallelic variants, further increasing the diagnostic yield of WGS.[12] RNA sequencing (transcriptomics) would support variant interpretation by demonstrating aberrant splicing or altered gene expression, particularly for variants in non-coding regions, which are often difficult to interpret.[13]

Epigenetic profiling, including methylation episignatures, can assist in the diagnosis of imprinting disorders and certain neurodevelopmental disorders associated with altered epigenetic regulation (such as Sotos syndrome, Kabuki syndrome, CHARGE syndrome, and Cornelia de Lange syndrome),[14] and is currently available in the mainstream NHS practice in selected settings to aid in the interpretation of VUS, but could also be used in the future for identification of genetic diagnoses in cases with negative initial WGS results.

Multi-omics approaches that integrate genomic, transcriptomic, epigenomic, and phenotype data are increasingly used in research settings and may in the future be integrated into mainstream practice to increase the diagnostic yield in developmental disorders, especially when standard testing remains inconclusive.[15] Integration of these technologies into mainstream clinical practice will require close collaboration between genomic laboratory and clinical services to ensure appropriate use and interpretation.

Sustained investment in workforce including specialist nurses or genomic practitioners for consenting and co-ordinating trio sample collections, education and training will be critical to support paediatricians in navigating evolving genomic pathways. Access to specialist advice, clear referral pathways, and continued genomic and non-genomic workforce development will help ensure genomic advances translate into impactful clinical benefit for children and families. ◆

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FURTHER READING

USEFUL LINKS AND RESOURCES

Education

National Genomic Education Programme and GeNotes learning resource, www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/

NHS genomic frameworks

Service map of clinical genetic services and associated GLHs, www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/clinical-genetics-departments-map/

National Genomic Test Directory, www.england.nhs.uk/publication/national-genomic-test-directories/

Genomic Medicine Service, www.england.nhs.uk/genomics/nhs-genomic-med-service/

NHS GMS PanelApp, https://nhsgms-panelapp.genomicsengland.co.uk/

Exeter GLH for rapid WGS indications, www.exeterlaboratory.com/genetics/genome-sequencing/

Gene interrogation and specific gene guides

DECIPHER database, www.deciphergenomics.org/

OMIM, www.omim.org/

GeneReviews, www.ncbi.nlm.nih.gov/books/NBK1116/

Orphanet, www.orpha.net/

Patient and family support

Genetic alliance UK, https://geneticalliance.org.uk/

Unique - Rare Chromosome Disorder Support Group, https://rarechromo.org/

Metabolic Support UK, https://metabolicsupportuk.org/

SWAN UK (Syndromes Without A Name), https://geneticalliance.org.uk/support-and-information/swan-uk-syndromes-without-a-name/

Other

British Inherited Metabolic Disease Group, https://bimdg.org.uk/guidelines/generation-study/

Deciphering Developmental Disorders study, www.ddduk.org.

100, 000 Genomes Project (100Kgp), www.genomicsengland.co.uk/initiatives/100000-genomes-project.

Practice points

- WGS is becoming first-line testing for many children with developmental disorders, replacing fragmented historical pathways and improving diagnostic yield
- A negative or uncertain result does not exclude a genetic diagnosis. Re-analysis, evolving phenotypes, and expanding gene discovery mean diagnoses may emerge over time
- Genomic testing complements holistic clinical care. Careful phenotyping, timely additional investigations, and multidisciplinary collaboration remain essential to maximise diagnostic utility and avoid common pitfalls
- Future advances (long-read sequencing, transcriptomics, epigenetics and multi-omics) are likely to increase diagnostic precision, requiring continued workforce education and strong clinical—laboratory partnerships